

association of these 2 conditions is well documented, as seen in this case report as well as earlier case reports.

## Conclusion

Acute HBV infection is rarely associated with GBS. Because early diagnosis and timely administration of IVIG or PE improve the degree of neurologic recovery, gastroenterologists should be aware of this association.

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# Review

## Extrahepatic Manifestations of Acute Hepatitis B Virus Infection

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Hepatitis B virus (HBV) infection leads to a number of hepatic complications, including acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although uncommon, several immune-mediated extrahepatic manifestations may develop during both acute and chronic HBV infection.

## Presentation of Hepatitis B Virus Infection

HBV infection leads to a wide spectrum of liver disease, including acute hepatitis, fulminant liver failure, chronic hepatitis, cirrhosis, and hepatocellular carcinoma.<sup>1</sup> Acute

HBV infection is often a mild, asymptomatic, subclinical illness that frequently passes without detection in approximately two thirds of cases.<sup>2</sup> Symptoms of acute HBV infection are often nonspecific, and diagnosis is secured through serologic testing for immunoglobulin (Ig) M antibody to hepatitis B core antigen. Clinical evidence of hepatitis—fatigue, nausea, or worse (jaundice and, occasionally, acute liver failure)—develops in approximately one third of patients with acute HBV infection. The time frame for clinical incubation of acute HBV infection averages 2–3 months; however, this time frame can range from 1–6 months after exposure. There is some evidence that the time of incubation correlates with the size of the viral load.<sup>3</sup> Rarely, acute and chronic HBV infection can be associated with extrahepatic conditions.

## Extrahepatic Manifestations

Although HBV primarily affects hepatocytes, it has also been shown to cause complications in other organs. Several of these manifestations have been described, and several of them are now well established.<sup>4</sup> These extrahepatic manifestations are nonspecific for HBV infection. Table 1 provides an overview of the distinct conditions for which HBV is the specific etiology. The pathophysiology of these associated symptoms is mainly based on immune complex reactions that occur in the skin, joints, muscles, and kidneys. Awareness and recognition of these manifestations are of the highest importance for facilitating early diagnosis and treatment.<sup>5</sup>

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**Table 1.** Extrahepatic Manifestations of Hepatitis B Virus Infection

Syndrome	Manifestations
Serum sickness–like syndrome	Fever (<39°C), erythematous skin rash, myalgias, arthralgias, fatigue/malaise
Glomerulonephritis	Membranous glomerulonephritis, membranoproliferative glomerulonephritis, immunoglobulin A–mediated nephropathy
Polyarthritis	Acute and symmetric inflammation, morning stiffness
Polyarteritis nodosa	Primary systemic necrotizing vasculitis, high fever, weakness, malaise, loss of weight and appetite
Dermatologic condition	Bullous pemphigoid, lichen planus, Gianotti-Crosti syndrome
Cryoglobulinemia	Common: Raynaud phenomenon, arthritis, sicca syndrome Less common: renal, neurologic, or vasculitic complications
Neurologic/psychological condition	Guillain-Barré syndrome, altered mental status, depression/psychosis

**Serum Sickness–Like Syndrome**

A transient serum sickness–like syndrome develops in 10–20% of patients with acute HBV infection.<sup>6</sup> As indicated above, symptoms precede the onset of jaundice by a few days to 4 weeks and subside after the onset of jaundice; however, these symptoms may be present throughout the course of the disease. Clinical manifestations include fever (<39°C), skin rash (erythematous, macular, maculopapular, urticarial, nodular, or petechial lesions), and polyarthritis, all of which usually resolve after recovery. The pathogenesis of this syndrome is thought to be due to circulating immune complexes composed of hepatitis B surface antigen (HBsAg) with subsequent consumption of complement.<sup>7</sup>

**Glomerulonephritis**

The incidence of HBV glomerulonephritis ranges from 0.1% to 25%.<sup>8–10</sup> Brzosko and colleagues were the first researchers to describe HBV involvement in the pathogenesis of glomerulonephritis, and they found the incidence of HBV to be 34.6% in various types of glomerular disease.<sup>11</sup> There are various types of glomerulonephritis associated with HBV infection; the most commonly known type is membranous glomerulonephritis (MGN). The clinical presentation of HBV-related MGN is usually a nephrotic syndrome, which may result in proteinuria, chronic renal failure, and hypertension in asymptomatic cases.

**Membranous Glomerulonephritis** MGN often occurs in children (predominantly males), and it is most often seen in HBV endemic areas of the world. When this condition occurs in adults, it is most commonly found in patients aged 30–50 years. Progressive chronic renal failure develops in approximately 50% of adults with MGN.<sup>12</sup> The disease is usually self-limited, lasting for months to years, particularly in children. The diagnosis of

HBV-associated MGN is made by the presence of at least 1 HBV antigen in renal tissue and the lack of other causes of glomerulonephritis. Resolution is usually marked by hepatitis B e antigen seroconversion to hepatitis B e antibody. MGN involves only the basement membrane, not the mesangium. The hallmark of MGN's pathophysiology is the collection of immune complexes within the basement membrane, which triggers a complement response. This forms a membrane attack complex on glomerular epithelial cells, which triggers an inflammatory process that causes capillary disruption.

**Membranoproliferative Glomerulonephritis** Membranoproliferative glomerulonephritis (MPGN) involves both the basement membrane and mesangium, unlike MGN. This process is marked by mesangial and capillary wall deposition of HBsAg and occurs via immune complexes that contain HBV antigens. Particularly when the viral infection is persistent, an increased immune response leads to the formation of immune complexes, and histology shows HBsAg deposits in the glomerular basement membrane.<sup>13</sup> When viewed under a microscope, the mesangium is expanded, and the glomerular basement membrane takes on a tram track–like appearance.

**Immunoglobulin A Nephropathy** IgA nephropathy has been shown to develop with concomitant IgG subepithelial deposits.<sup>14</sup> In addition to subepithelial deposits seen with electron microscopy, tubuloreticular inclusions have been reported within the cisternae of the endoplasmic reticulum of the endothelial cell cytoplasm of glomerular and peritubular capillaries. IgA nephropathy has typically been regarded as a benign disease with an indolent evolution, with more aggressive forms resulting in extensive crescent disease that presents as acute renal failure. Progression to chronic renal failure is usually slow and progressive if the patient does not recover.

***Polyarteritis Nodosa***

Generalized necrotizing vasculitis was first reported in 1970 in association with hepatitis B antigenemia.<sup>15,16</sup> The exact incidence of HBV-associated polyarteritis nodosa (PAN) is unknown, although it is estimated to range from 30–70%.<sup>17,18</sup> PAN is a primary systemic necrotizing vasculitis, and infection characterized by HBsAg positivity can result in a vasculitis that takes the form of PAN. Clinical symptoms for PAN and HBV-related PAN are the same, except for orchitis.<sup>19</sup> Symptoms result from ischemic damage to the affected organs/systems, such as the skin, heart, kidneys, and nervous system. Generalized symptoms include fever, weakness, malaise, loss of appetite, and weight loss. Skin findings can range from palpable purpura to nodules and erythematous rashes. In several studies, clinical remission of PAN has been observed in patients who were treated with interferon and in very few or no patients who did not receive the treatment.<sup>19,20</sup> The HBV genome has not revealed mutations associated with PAN and, therefore, is attributed to immune complex deposition with antigen excess.

***Dermatologic Conditions***

There are several cutaneous disorders associated with HBV infection, typically related to immune complex deposition. Rashes associated with chronic HBV infection are more likely to have palpable purpura, which is associated with neutrophil infiltration that leads to small vessel necrosis.

**Bullous Pemphigoid** Bullous pemphigoid (BP), which is classified as a type II hypersensitivity reaction, is an acute or chronic autoimmune skin disorder that leads to the formation of bullae between the layers of the dermis and epidermis. This skin disorder is often detected in elderly patients and is known to occur following various vaccines (with BP's association with the tetanus toxoid booster being particularly well documented). A case study reported the development of BP in a child following immunization for HBV.<sup>21</sup> This case led to the postulation that HBsAg can function as a trigger for inducing nonspecific immune reactivation or by stimulating specific antibody production that may cross-react with BP antigens.<sup>21</sup>

**Lichen Planus** In a 2005 Turkish study, oral lichen planus was found to have a high prevalence in patients with HBsAg positivity.<sup>22</sup> A mechanism for this condition has not been determined, and its absolute prevalence is unknown. This dermatologic disorder typically affects the oral mucosa, tongue, and skin, forming papules and lesions that resemble lichen. Lichen planus has the characteristic appearance of skin "lichenification," which often resembles the bark of a tree. The epidermis may be atrophic, normal, or hypertrophic, and there is often degeneration or liquefaction of the deeper basal layer, which can lead to vesicles.

**Gianotti-Crosti Syndrome** Also known as papular acrodermatitis of childhood, this syndrome is characterized by small, flat, erythematous, papular eruptions that appear on the face and extremities. HBV and Epstein-Barr virus are the most frequently associated viruses, although other reported etiologies have been attributed to hepatitis A virus, non-A or B hepatitis virus, cytomegalovirus, coxsackie, adenovirus, enterovirus, HIV, and others.<sup>23</sup> The association of Gianotti-Crosti syndrome with HBV infection has been reported as early as 1976.<sup>24</sup> This syndrome typically affects infants and young children and is characterized by a papular or papulovesicular rash that occurs mainly on the face and distal 4 extremities.

***Cryoglobulinemia***

The presence of HBV infection has been known to cause the reversible precipitation of immunoglobulins in a cold environment. There are 3 types of cryoglobulins; type II (monoclonal IgM and polyclonal IgG) and type III (polyclonal IgM and monoclonal IgG) are classified as essential and are found in patients with chronic HBV infection. The prevalence of cryoglobulinemia ranges from 0–15%.<sup>25,26</sup> Purpura and arthralgias are the first and second most common presenting features, respectively. Cryoglobulinemia is commonly associated with Raynaud phenomenon, arthritis, and sicca syndrome and can lead to renal, neurologic, and vasculitic complications. The important difference between cryoglobulin-induced vasculitis and PAN is that the latter condition produces arterial aneurysms and peripheral eosinophilia, whereas the former condition is associated with only small vessels.

***Guillain-Barré Syndrome***

Guillain-Barré syndrome (GBS) has been associated with both acute and chronic HBV infection; however, this syndrome is rare, comprising fewer than 20 reported cases to date. In patients with neuropsychiatric disorders and HBV infection, both HBsAg and HBV DNA have been detected in cerebrospinal fluid, and it is uncertain whether the virus itself or an immune-mediated reaction is responsible for these symptoms of the central nervous system. The case of acute HBV infection associated with GBS that was reported by Yimam and colleagues highlighted the need for awareness of this rare association, the basic pathophysiology associated with this syndrome, and the importance of prompt recognition and timely initiation of therapy.<sup>27</sup> Although peripheral neuropathy has been described, it has been seen mainly in cases of chronic HBV infection, making the case report by Yimam and associates unusual and worthy of a report.<sup>27,28</sup>

As discussed by Yimam and colleagues, recovery is contingent upon early diagnosis in order to begin treatment with either intravenous immunoglobulin (IVIG) or

plasma exchange (PE).<sup>27</sup> Large, randomized, multicenter studies have established the effectiveness of PE in patients with severe GBS.<sup>29,30</sup> In an updated meta-analysis of 6 randomized, controlled trials (with a total of 649 patients with GBS), treatment with PE was superior to supportive care.<sup>31</sup> The patient in the case report by Yimam and colleagues was treated with IVIG, which has been shown to be as effective as PE for the treatment of GBS.<sup>27</sup> This conclusion was made by a 2012 systematic review and meta-analysis and is the current treatment guideline by the American Academy of Neurology.<sup>32,33</sup> Other care options for GBS include supportive care, cardiovascular management, pain control, and rehabilitation. The mainstay treatment of glucocorticoids has not shown a benefit in the treatment of patients with GBS.<sup>34</sup>

As both IVIG and PE have a role in the treatment of acute HBV-related GBS, this would imply that the mechanism explaining this is similar to that of GBS, in which there is immune-mediated damage to the myelin sheath. Consistent with the other extrahepatic manifestations of HBV infection, the most likely pathophysiologic explanation lies with an antibody-mediated attack of the central nervous system, which results in either direct assault or perhaps a vasculitis-related insult to the myelin sheath.<sup>35</sup>

## Conclusion

Although HBV infection is recognized as affecting hepatocytes, it is important to be aware of the spectrum of extrahepatic manifestations associated with this infection. The association of acute HBV infection and GBS that was reported by Yimam and coworkers has been rarely described; therefore, it is important to bring awareness to both timely diagnostic and therapeutic methods.<sup>27</sup> The common denominator of all of these extrahepatic manifestations appears to be linked to the formation of the antigen-antibody immune complex.

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